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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,859	01/07/2002	Qihong Huang	087102 0272537	5405

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 01/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,859	HUANG ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2005 and 24 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,44,46 and 70-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,44,46 and 70-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed October 24, 2005, is acknowledged and has been entered.

2. The amendment filed June 23, 2005, is acknowledged and has been entered. Claims 20-43, 45, and 47-69 have been canceled. Claims 1, 9, 13, 16, 44, and 46 have been amended. Claims 70-96 have been added.

3. Claims 1-19, 44, 46, and 70-96 are pending in the application and are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Allowable Subject Matter

5. With regard to the preceding Office action mailed February 16, 2005, the indicated allowability of claims 7 and 8 is withdrawn in view of the new grounds of rejection of those claims, which is set forth herein.

Priority

6. Applicant's claim under 35 USC § 119(e) for benefit of the earlier filing date of the U.S. Provision Application Serial No. 60/260,478, filed January 8, 2001, is acknowledged.

However, claims 1-19, 44, 46, and 70-96 do not properly benefit under 35 U.S.C. § 119(e) by the earlier filing date of the priority document claimed, since those claims are rejected below under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional

application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely January 7, 2002.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed June 23, 2005, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed February 16, 2005.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

8. The rejection of claims 1-19, 44, 46, and 70-96 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in section 9 of the preceding Office action mailed February 16, 2005, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At pages 19-21 of the amendment filed June 23, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the preceding Office action at page 7, paragraph 2, this issue may is remedied by amending the claims, such that the breadth of the claims is limited to a nucleic acid comprising SEQ ID NO: 1, or alternatively to a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1 and encoding a polypeptide comprising SEQ ID NO: 2 or a polypeptide having or

retaining a disclosed, particularly identifying functional property of the polypeptide of SEQ ID NO: 2 that correlates with a particularly identifying structural feature common among the members of the genus of polypeptides encoded by the nucleic acid molecule of SEQ ID NO: 1 and the other nucleic acids also encompassed by the claims.

Rather than limiting the claims to a nucleic acid comprising the polynucleotide sequence of SEQ ID NO: 1, or alternatively to a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1 and encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, Applicant has attempted to remedy this issue by amending the claims to recite the polypeptide encoded by members of the structurally variant genus of nucleic acids inhibit the activity of a caspase. However, the specification merely teaches one species of polypeptide (i.e., the polypeptide of SEQ ID NO: 2), which inhibits the activity of a caspase, namely the activity of caspase-9, as opposed to any other caspase, and inhibits Bax-induced apoptosis, as opposed to any other apoptotic pathway (e.g., Fas-induced apoptosis). Moreover, the specification teaches this species of polypeptide is not capable of inhibiting the activity of other caspases, such as caspase-3, caspase-7, and caspase-8, and is not capable of inhibiting Fas-induced apoptosis; see, e.g., paragraph [0032] of the published application (page 9, line 26, through page 10, line 6 of the specification, as filed).

Furthermore, although the specification teaches that both the "BIR1 domain" (i.e., amino acids 74-140 of SEQ ID NO: 2) and the "BIR2 domain" (i.e., amino acids 182-249 of SEQ ID NO: 2) of BmIAP (i.e., the polypeptide of SEQ ID NO: 2), together with the "RING domain" (i.e., amino acids 298-314 of SEQ ID NO: 2) of the protein, are each required to inhibit Bax-induced apoptosis and/or inhibit the activity of caspase-9 (page 33, line 3, through page 34, line 2), only claims 73, 78, 83, 89, and 95 are specifically directed to nucleic acid molecules encoding polypeptides comprising amino acids 182-249, amino acids 182-249 of SEQ ID NO: 2, and amino acids 298-314 of SEQ ID NO: 2. Claims 72, 77, 82, 88, and 94 are directed to nucleic acids encoding polypeptides comprising domains that have the function of the domains of amino acids 182-249, amino acids 182-249 of SEQ ID NO: 2, and amino acids 298-314 of SEQ ID NO: 2, not

necessarily to nucleic acids encoding polypeptides sharing any particularly identifying (i.e., substantial) structural feature. Accordingly, claims 1-19, 44, 46, 70-72, 74-77, 79-82, 84-88, 90-94, and 96 are directed to a genus of structurally varying nucleic acid molecules that encode structurally and functionally varying polypeptides, which commonly share the ability to inhibit the activity of a member of the genus of caspases.

With regard to claims (e.g., claim 1) that are directed to nucleic acid sequences encoding a polypeptide comprising only one, but not necessarily both, of a domain having the function of "the BIR1 domain" and a domain having the function of "the RING domain", which do not necessarily also comprise a domain having the function of "the BIR2 domain", inasmuch it cannot be determine to which of such domains the claim refers, the skilled artisan could not immediately envision, recognize or distinguish such polypeptides comprised of these domains, and therefore could not immediately envision, recognize or distinguish the nucleic acids that encode those proteins. Moreover, because the functions of these domains to which the claims refer have not been described with clarity and particularity, the skilled artisan could not immediately envision, recognize or distinguish polypeptides comprised of domains having the function of such inadequately defined domains.

Given the disclosed functional limitations of the polypeptide of SEQ ID NO: 2 (e.g., its inability to inhibit caspase-3), it is apparent that only disclosed species of polypeptide encoded by the only disclosed nucleic acid is not reasonably deemed representative of the genus, as a whole, of nucleic acids encoding polypeptides having varying structures but commonly inhibiting a caspase.

Although claims 73, 78, 83, 89, and 95 are specifically directed to nucleic acid molecules encoding polypeptides comprising amino acids 182-249, amino acids 182-249 of SEQ ID NO: 2, and amino acids 298-314 of SEQ ID NO: 2, none of these particular structural elements, or the combination thereof, has been correlated with the ability of the polypeptides encoded by the claimed nucleic acid molecules to inhibit the activity of any one member of the genus of caspases. Again, as explained above, even the polypeptide of SEQ ID NO: 2, which comprises the combination of these structural elements is capable of inhibiting the activity of any caspase, as the specification

teaches the polypeptide inhibits only the activity of caspase-9 without effecting the activity of any of caspases-3, -7, or -8 (see, e.g., page 35, line 24, through page 36, line 2). Accordingly, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed because the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the genus of nucleic acid sequences to which the claims are directed.

For clarity claims 7 and 8 have been newly included herein because the claims are directed to an isolated or recombinant nucleic acid encoding a polypeptide having "a sequence" (i.e., at least 2 contiguous amino acids) of the amino acid sequence of SEQ ID NO: 2, or comprising "a nucleic acid sequence" (i.e., at least 2 contiguous nucleotides) of the polynculeotide sequence of SEQ ID NO: 1. As such, claims 7 and 8 are broadly but reasonably interpreted to encompass any member of a very large genus of structurally and functionally disparate nucleic acid molecules, which are only required have in common with a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 1 a sequence of at least contiguous nucleotides, or a sequence that encode at least 2 contiguous amino acids of the amino acid set forth as SEQ ID NO: 2. Moreover, claims 7 and 8 are not directed to a genus of nucleic acids that commonly share a particularly identifying (i.e., substantial) structural feature that correlates with any particularly identifying functional feature that is also shared by at least most of the members of the genus.

Although claims directed to nucleic acid molecules encoding variants of the polypeptide of SEQ ID NO: 2, which comprise amino acid sequences that are at least 95% identical to the amino acid sequence of SEQ ID NO: 2, and are capable of inhibiting the activity of a caspase, may find literal support in the specification, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can

> recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

In this instance, the specification does not adequately describe variants of the polypeptide of SEQ ID NO: 2, which comprise amino acid sequences that are at least 95% identical to the amino acid sequence of SEQ ID NO: 2, and are capable of inhibiting the activity of any member of the genus of caspases (e.g, caspase-3), since the specification teaches the only disclosed member of the genus (i.e, the polypeptide of SEQ ID NO: 2) is only effective to inhibit the activity of capase-9, and not the activity of any of caspases-3, -7, and -8.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). Given the similarity in the structures of BmIAP and XIAP, which are discloses as having markedly different activities (see, e.g., paragraph [0100] of the published application), it is submitted that the skilled artisan could not predict whether any given protein encoded by a nucleic acid sequence encompassed by the claims, which appears to be structurally related to the polypeptide of SEQ ID NO: 2, would have the ability to inhibit the activity of a caspase, and could not envision, recognize or distinguish members of the genus of polypeptides encoded by these nucleic acid sequences, given only the instant disclosure.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, as in that, there is no language that adequately describes the genus of nucleic acid sequences that are encompassed by the claims,

which encode polypeptides having the ability to inhibit the activity of a caspase. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Furthermore, the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to inhibit the activity of a caspase, or the onset of apoptosis, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding the nucleic acid sequences that encode polypeptides having the claimed activities; without such a nucleic acid sequences, it is impossible to practice the invention, and a specification that does not reasonably enable the skilled artisan to make and use the claimed invention cannot have adequately described the invention to reasonably convey its possession by Applicant at the time the application was filed.

Although the skilled artisan could potentially identify nucleic acid sequences that might be used in practicing the claimed invention by screening polypeptides encoded by

these sequences to determine if, for example, they are capable of inhibiting the activity of a caspase, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify structurally related nucleic acid sequences encoding polypeptides that inhibit the activity of a caspase.

Accordingly, it is believed that each of Applicant's arguments has been addressed; and though carefully considered, none have been found persuasive.

9. The rejection of claims 1-6, 9-11, 13-19, 44, and 46 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1 and encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an expression cassette comprising the polynucleotide sequence of said nucleic acid molecule, an isolated transformed cell comprising said nucleic acid molecule, an array comprising said nucleic acid molecule, and a method for producing a recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 comprising expressing said nucleic acid molecule, **does not reasonably provide enablement for making and using** a nucleic acid molecule comprising a sequence

that is not identical to SEQ ID NO: 1 or encoding a polypeptide comprising an amino acid sequence that is not identical to SEQ ID NO: 2, or an expression cassette comprising the polynucleotide sequence of said nucleic acid molecule, or a transformed cell comprising said nucleic acid molecule, an array comprising said nucleic acid molecule, or a method for producing a recombinant polypeptide comprising expressing said nucleic acid molecule, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

At pages 22-36 of the amendment filed June 23, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has contended that the Office has failed to establish a *prima facie* case for rejecting the claims being as not reasonably enabled by the disclosure, since no objective evidence has been provided to show the skilled artisan could not make and/or use the claimed invention without undue and/or unreasonable experimentation.

In reply, MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the

art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In this instance, the specification provides ample factual evidence that the amount of guidance, direction and exemplification disclosed in the specification would not be sufficient to have enabled the skilled artisan, at the time the application was filed, to make and/or use the claimed invention without undue and/or unreasonable experimentation. As explained in the rejection of claims under 35 U.S.C. § 112, first paragraph, as containing subject matter not adequately described, the claims are directed to a broad genus of structurally and functionally disparate nucleic acid sequences encoding structurally and functionally different polypeptides that share the ability to inhibit the activity of a caspase. Although the specification teaches the polypeptide of SEQ ID NO: 2 (i.e., BmIAP) inhibits the activity of caspase-9, it also teaches the polypeptide is *not* capable of inhibiting the activity of any of caspases-3, -7, and -8. Furthermore, although the specification teaches the polypeptide of SEQ ID NO: 2 is capable of inhibiting the Bax-induced apoptosis, it also teaches the polypeptide is not capable of inhibiting Fas-induced apoptosis. In contrast, the specification discloses XIAP, which is allegedly the human homolog of BmIAP, is capable of inhibiting both apoptotic pathways; see, e.g., paragraph [0100] of the published application (page 34, lines 14-28, of the specification, as filed).

The claims are directed to nucleic acid sequences encoding variants of the polypeptide of SEQ ID NO: 2, which commonly have the ability to inhibit the activity of a caspase, but not necessarily caspase-9. Accordingly, the claims encompass nucleic acid sequences encoding variants of the polypeptide of SEQ ID NO: 2, which inhibit the activity of caspase-3, for example. The specification, however, does not teach the skilled artisan, for example, to convert the polypeptide of SEQ ID NO: 2, or variants thereof encoded by the nucleic acid sequences to which the claims are directed, into a

polypeptide, such as XIAP, which is capable of inhibiting caspase-3, as well as caspase-9.

Furthermore, although the specification teaches that the "BIR1 domain", the "BIR2" domain", and the "RIING domain" of BmIAP are essential to its ability to inhibit the activity of caspase-9, the claims are directed to nucleic acid molecules encoding polypeptides that comprise only one of these domains, or to polypeptides that comprise variants of these domains, or to polypeptides comprising domains that have only the function, but not necessarily the structure, of these domains. The specification does not clearly and particularly teach the function of the "BIR1 domain", the "BIR2" domain", and the "RIING domain" of BmIAP, nor does it teach the skilled artisan to recognize structurally disparate domains that have the functions of these domains. Although the polypeptides encoded by the nucleic acid sequences to which the claims are directed do not necessarily comprise variants of the "BIR1 domain", the "BIR2" domain", and the "RIING domain" of BmIAP, per se, it is noted that the specification fails to teach which amino acids of these domains of BmIAP are essential to their function. The specification also fails to teach by which other amino acids these essential amino acids are replaced without loss of those functions.

Accordingly, given the disclosures of the references cited in the preceding Office action, which establish the state of the art, the level of skill in the art, and the unpredictability in the art it is apparent, even given the instant disclosure, together with the knowledge and skill of the artisan at the time the application was filed, the skilled artisan could not make and/or use the claimed invention without undue and/or unreasonable experimentation.

Applicant's arguments set forth at pages 19-36 are acknowledged and have been carefully considered, but reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

"Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

The overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify nucleic acid sequences encoding polypeptides that are variants of the polypeptide of SEQ ID NO: 2 that have the common ability to inhibit the activity of a caspase, which can be used to make and/or use the claimed invention; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, although Applicant's arguments have been carefully considered, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence indicating the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections – 35 USC § 102

10. The rejection of claims 1-8, 13, 15, 16, 19, 46, 70-73, 79-83, and 90-95 under 35 U.S.C. 102(b) as being anticipated by Fatyol et al. (of record), as evidenced by Huang et al. (of record), the USPTO search report "us-10-041-859-2.rge" (result 1 of the "Alignments"), and the USPTO search report "us-10-041-859-1.rge" (result 1 of the "Alignments"), is maintained.

At pages 36-38 of the amendment filed June 23, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 13, 15, 16, 19, and 79-83 read on the transformed *Bombyx mori* cell line disclosed by the prior art, since, as evidenced by Huang et al. (of record), the USPTO search report "us-10-041-859-2.rge" (result 1 of the "Alignments"), and the USPTO search report "us-10-041-859-1.rge" (result 1 of the "Alignments"), the cell line comprises a nucleic acid sequence encoding the disclosed polypeptide of SEQ ID NO: 2 (i.e., BmIAP). Notably, claims 13, 15, 16, 19, and 79-83 are not limited to a transformed cell that is "transformed" with the nucleic acid sequence encoding this polypeptide.

The polypeptide of SEQ ID NO: 2, which is expressed naturally in the transformed cell line disclosed by the prior art, has all of the features recited in the claims.

As explained more thoroughly below in the rejection of claims 1-8 and 70-73 under 35 U.S.C. § 101, claims 1-8 and 70-73 are directed to subject matter that is indistinguishable from a naturally occurring nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, such as the gene and its transcript (i.e., messenger RNA (mRNA) molecule) encoding the polypeptide of SEQ ID NO: 2, of which the transformed *Bombyx mori* cells disclosed by the prior art are naturally comprised. Notably claims 1-8 and 70-73 are not limited to "isolated" nucleic acids, but rather specifically encompass "recombinant' nucleic acids, which, as explained below, are indistinguishable from the naturally occurring nucleic acids of which the cell line is comprised. Accordingly, claims 1-8 and 70-73 have been newly added to this rejection.

Claims 46 and 90-95 have been newly included herein since these claims are directed to a method for making a recombinant polypeptide comprising only the step of expressing a polynucleotide sequence that encodes, for example, the polypeptide of SEQ ID NO: 2. As explained, the transformed cell line, which is disclosed by the prior art, expresses a polynucleotide sequence that encodes the polypeptide of SEQ ID NO: 2; therefore, because the prior art teaches culturing these cells, the process disclosed

by the prior art is deemed the same as the claimed process. Notably the recombinant polypeptide that is produced using the claimed process is not necessarily the polypeptide of SEQ ID NO: 2, or the polypeptide encoded by the nucleic acid sequence of which the transformed cell line is necessarily comprised. It is aptly noted the prior art teaches the cultured cells produced a recombinant polypeptide (i.e., puromycin *N*-acetyl transferase); see, e.g., the abstract. Of course, even if the "recombinant" polypeptide produced by the claimed process necessarily the polypeptide of SEQ ID NO: 2, given the definition of the term "recombinant" set forth below, it is not apparent that such a limitation would distinguish the claimed process from the process disclosed by the prior art.

For clarity, although claims 9-12, 74-78, and 96, which are directed to expression cassettes, might arguably be rejected herein, these claims were excluded from this rejection because, in light of the specification, it is believed it would have been unreasonable to interpret those claims as if directed to the expression cassette of which the transformed *Bombyx mori* cell line (as disclosed by the prior art) is comprised, as opposed to an expression cassette comprising a polynucleotide sequence encoding BmIAP (as claimed). On the other hand, claims 1-8, 13, 15, 16, 19, 46, 70-73, 79-83, and 90-95 are broadly but reasonably interpreted in light of the specification to read on the nucleic acids, the cells, or the processes of the prior art, since it is not immediately evident that they are distinguishable from the subject matter that is claimed.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

11. Claims 1-8 and 70-73 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-8 and 70-73 are specifically drawn to an "isolated or recombinant" nucleic acid comprising a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1, or encoding a polypeptide having a sequence set forth in SEQ ID NO: 2. The recombinant nucleic acids to which the claims are directed are not necessarily isolated.

Merriam-Webster's Online Dictionary, 10th Edition (copyright © 2005 by Merriam-Webster, Inc.) defines "recombinant" as "relating to or exhibiting genetic recombination".

Given this definition, it is not apparent that the subject matter of claim 7 is distinguishable from a naturally occurring nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, such as the gene and its transcript (i.e., messenger RNA (mRNA) molecule) of which *Bombyx mori* cells are naturally comprised, which encode the polypeptide of SEQ ID NO: 2. It is also not apparent that the subject matter of claims 1-6, 8, and 70-73 is distinguishable from such naturally occurring nucleic acid molecules because the claims merely require the nucleic acid to comprise *a nucleic acid sequence* having at least 95% identity to SEQ ID NO: 1. Moreover, the nucleic acids of claims 1-6, 8, and 70-73 do not necessarily comprise the polynucleotide sequence of SEQ ID NO: 1, but only at least 2 contiguous nucleotides that are identical to SEQ ID NO: 1. Both the gene and its transcript encoding the polypeptide of SEQ ID NO: 2, which occur naturally in *Bombyx mori* cells, comprise such a sequence that is at least 95% identical to SEQ ID NO: 1. Accordingly, giving the claims the broadest, reasonable interpretation that is consistent with both the specification and that which the skilled artisan would have, the claims are drawn to non-statutory subject matter (i.e., a naturally occurring product).

This issue can be remedied by amending claims 1-8 and 70-73 such that they are solely directed to "isolated", as opposed to "recombinant", nucleic acid molecules.

12. Claims 1-14, 19, 46, 70-83, and 90-96 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-8 and 70-73 are specifically drawn to an "isolated or recombinant" nucleic acid comprising a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1, or encoding a polypeptide having a sequence set forth in SEQ ID NO: 2. Claims 9-12, 74-78, and 96 are drawn to an expression cassette comprising at least one nucleic acid operably linked to a promoter, wherein the nucleic acid comprises a sequence having at least 95% identity to SEQ ID NO: 1, or encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. Claims 13, 14, 19, and 79-83 are drawn to a transformed cell, including a mammalian cell, or more particularly a human cell, comprising a nucleic acid comprising a sequence having at least 95% identity to SEQ ID NO: 1, or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. Claims 46 and 90-95 are drawn to methods for making a recombinant polypeptide comprising a step of expressing a nucleic acid encoding the polypeptide.

Notably, the recombinant nucleic acids, expression cassettes, and transformed cells to which the claims are directed are not necessarily isolated; and the methods for making recombinant polypeptide are not necessarily performed *in vitro* using cultured cells.

As noted in the rejection of claims 1-8 and 70-73 under 35 U.S.C. § 101 above, Merriam-Webster's Online Dictionary, 10th Edition (copyright © 2005 by Merriam-Webster, Inc.) defines "recombinant" as "relating to or exhibiting genetic recombination", but the dictionary also defines "recombinant" as "relating to or containing recombinant DNA" (copyright © 2005 by Merriam-Webster, Inc.).

Given either of these definitions, because claims 1-14, 19, 46, 70-83, and 90-96 are drawn to recombinant polynucleotides, expression cassettes, and transformed cells, *which are not necessarily isolated*, and methods for making recombinant polypeptides, which do not necessarily comprise culturing isolated transformed cells comprising nucleic acid molecules encoding those polypeptides, the claims are broadly but reasonably interpreted to encompass such products that are present in cells, which are

not isolated but rather comprised *within* an organism, including a human, or such processes that are performed *in vivo* within an organism, including a human.

Support for this interpretation of the claims is found throughout the specification; see, e.g., paragraphs [0009]-[0011], [0055], [0063], and [0065]-[0074] of the published application.

MPEP § 2105 [R-1] states:

> If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.

This issue can be remedied by amending claims 1-8 and 70-73 such that they are solely directed to "isolated", as opposed to "recombinant", nucleic acid molecules, "isolated" expression cassettes, "isolated" transformed cells, and methods for making recombinant polypeptides comprising *culturing isolated* cells comprising the nucleic acid molecules encoding the polypeptides.

13. Claims 1-6, 9-19, 44, 46, 70-72, 74-77, 79-82, 84-88, and 90-95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 9-19, 44, 46, 70-71, 74-76, 79-81, 84-87, and 90-93 are indefinite because the claims recite, "wherein the isolated or recombinant nucleic acid encodes a polypeptide including therein at least one of: (1) a domain having the function of **the BIR1 domain** and (2) a domain having the function of **the RING domain**" (emphasis added). There is no antecedent basis in the claims to support the recitation of the limitations, "the BIR1 domain" and "the RING domain". Accordingly, metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Claims 72, 77, 82, 88, and 94 are indefinite because the claims recite, "wherein "the domain having the function of the BIR1 domain encoded by the nucleic acid has the amino acid sequence of residues 74 to 140 of SEQ ID NO:2 **or a sequence related to** residues 74 to 140 of SEQ ID NO:2 by one or more conservative substitutions, the

domain having the function of the BIR2 domain encoded by the nucleic acid has the amino acid sequence of residues 182 to 249 of SEQ ID NO:2 **or a sequence related to** residues 182 to 249 of SEQ ID NO:2 by one or more conservative substitutions, and the domain having the function of the RING domain encoded by the nucleic acid has the amino acid sequence of residues 298 to 314 of SEQ ID NO:2 **or a sequence related to** residues 298 to 314 of SEQ ID NO:2 by one or more conservative substitutions" (emphasis added). It cannot be ascertained how the sequence of the domains having the functions of either the BIR1 domain, the BIR2 domain, or the RING domain are necessarily related to residues 74 –140, residues 182 –249, and 298-314 of SEQ ID NO: 2, respectively, *by one or more conservative substitutions*. Accordingly, the claims fail to delineate the subject matter that is regarded as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to determine infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

14. Claims 1-6, 9-19, 44, 46, and 70-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

The claims are directed to a genus of nucleic acid molecules comprising a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and encoding a polypeptide comprising a domain having the function of the BIR1 domain and/or a domain having the function of the RING domain, which inhibits the activity of a caspase.

Applicant has asserted that the amendment filed June 23, 2005, has not introduced new matter, and that support for the language of the claims, as amended, is found throughout the specification, including the claims, as originally filed. For example, Applicant has asserted support for the recitation in the claims of the domains (i.e., BIR1;

BIR2; and RING) of BmIAP is found at page 32, lines 19-25, and support for the recitation that the polypeptides inhibit the activity of a caspase is found at page 35, lines 24 and 25.

Contrary to Applicant's assertions, the specification, including the claims, as originally filed, does not provide proper and sufficient written support for the claims now directed to a genus of nucleic acid molecules comprising a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and encoding a polypeptide comprising a domain having the function of the BIR1 domain and/or a domain having the function of the RING domain, which inhibits the activity of a caspase.

The paragraph beginning at page 32, in line 19, to which Applicant has specifically referred, describes a particular nucleic acid molecule (i.e., the nucleic acid molecule of SEQ ID NO: 1), which encodes a particular protein (i.e., the polypeptide of SEQ ID NO: 2). This paragraph, however, does not describe the genus to which the present claims are drawn. Moreover, this disclosure does not describe variants of the nucleic acid molecule of SEQ ID NO: 1, which encode polypeptides comprising "a domain having the function of the BIR1 domain" and/or "a domain having the function of the RING domain" that have the ability to inhibit the activity of a caspase, or polypeptides comprising "a domain having the function of the BIR1 domain", "a domain having the function of the BIR2 domain", and "a domain having the function of the RING domain" that have the ability to inhibit the activity of a caspase.

Claims 1-6, 9-19, 44, 46, 70, 71, 74-76, 79-81, 84-87, 90-93, and 96, as opposed to claims 72, 73, 77, 78, 82, 83, 88, 89, 94, and 95, are not directed to nucleic acid molecules encoding polypeptides having any particular structural feature, rather only to nucleic acids encoding polypeptides comprising domains having the function of "the BIR1 domain", "the BIR2 domain", and/or "the RING domain". As the claims are not necessarily limited nucleic acid molecules encoding polypeptide comprising the "BIR1 domain", the "BIR2 domain", and/or the "RING domain" of the polypeptide of SEQ ID NO: 2, the nucleic acid molecules encode polypeptides comprising domains that remain structurally undefined. Furthermore, because the functions of the BIR1, BIR2, and RING domains of SEQ ID NO: 2 (i.e., the domains of amino acids 74-140, 182-249, and

298-314, respectively, of SEQ ID NO: 2) have not been clearly and particularly described, so as to permit the skilled artisan to immediately envision, recognize, or distinguish polypeptide comprising domains having the function of one or more of these domains, the claimed nucleic acid molecules encode polypeptides comprising domains that are functionally undefined.

The other specific disclosure to which Applicant has referred, which begins at page 35, in line 24, merely describes BmIAP (i.e., the disclosed polypeptide of SEQ ID NO: 2) as inhibiting the activity of caspase-9. This disclosure does not remedy the insufficiency of the other paragraph to which Applicant has specifically referred, as providing the necessary written support for the claim language. Moreover, it does not support claims drawn to a genus of variants of the nucleic acid molecule of SEQ ID NO: 1, which encodes variants of the polypeptide of SEQ ID NO: 2 having the ability to inhibit the activity of any one member of a genus of caspases (e.g., caspase-3, -6, 7, 8, and 9).

For clarity, claim 12 is included in this rejection because the claim is directed to the expression vector of claim 9, wherein the nucleic acid that encodes a polypeptide comprising an amino acid sequence (i.e., at least 2 contiguous amino acids) of SEQ ID NO: 2. Accordingly, the recitation of the limitation in claim 12 does not remedy the issue that has been raised above with respect to claim 9, as notably claim 12 is not limited to an expression vector comprising a nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, but only part thereof. The same is true of claims 19, 74, 79, 84, 85, 90, 91, and 96: The recitations of the limitations in these claims do not remedy the issues that has been raised above with respect to the prior claims, as notably claims 19, 74, 79, 84, 85, 90, 91, and 96 are not limited to nucleic acids, expression cassettes, transformed cells, or method for making recombinant polypeptide encoded by nucleic acids, which comprise a nucleic acid sequence comprising the polynucleotide sequence of SEQ ID NO: 1, or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, but only parts thereof (i.e., a nucleic acid sequence comprising at least 2 contiguous nucleotides of SEQ ID NO: 1, or encoding a polypeptide comprising at least 2 contiguous amino acids of SEQ ID NO: 2).

Claims 72, 77, 82, 88, and 94 are directed to a genus of nucleic acid molecules comprising a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and encoding a polypeptide comprising a domain having the function of the BIR1 domain, a domain having the function of the BIR2 domain, and a domain having the function of the RING domain, which inhibits the activity of a caspase, wherein "the domain having the function of the BIR1 domain encoded by the nucleic acid has the amino acid sequence of residues 74 to 140 of SEQ ID NO:2 or a sequence related to residues 74 to 140 of SEQ ID NO:2 by one or more conservative substitutions, the domain having the function of the BIR2 domain encoded by the nucleic acid has the amino acid sequence of residues 182 to 249 of SEQ ID NO:2 or a sequence related to residues 182 to 249 of SEQ ID NO:2 by one or more conservative substitutions, and the domain having the function of the RING domain encoded by the nucleic acid has the amino acid sequence of residues 298 to 314 of SEQ ID NO:2 or a sequence related to residues 298 to 314 of SEQ ID NO:2 by one or more conservative substitutions". However, again, there appears to be no written support for the claimed genus of nucleic acid molecules, as the specification does not describe variants of the nucleic acid molecule of SEQ ID NO: 1, which encode variants of the polypeptide of SEQ ID NO: 2 comprising domains having the function of the BIR1, BIR2, and RING domains of SEQ ID NO: 2 (i.e., the domains of amino acids 74-140, 182-249, and 298-314, respectively, of SEQ ID NO: 2), which each comprise amino acid sequences that differ from those domains of the polypeptide of SEQ ID NO: 2 by one or more conservative amino acid substitutions. While the specification, as originally filed, provides written support for a genus of nucleic acid molecules encoding variants of the polypeptide of SEQ ID NO: 2, which comprise amino acid sequences that are at least 95% identical to SEQ ID NO: 2 (see, e.g., page 16, lines 24 and 25), the specification does not describe nucleic acid molecules encoding variants of the polypeptide of SEQ ID NO: 2 comprising "variants" of the BIR1, BIR2, and RING domains of SEQ ID NO: 2 (i.e., the domains of amino acids 74-140, 182-249, and 298-314, respectively, of SEQ ID NO: 2), per se.

Claims 73, 78, 83, 89, and 95 are directed to a genus of nucleic acid molecules comprising a nucleic acid sequence having at least 95% sequence identity to SEQ ID

NO: 1 and encoding a polypeptide comprising a domain having the function of the BIR1 domain, a domain having the function of the BIR2 domain, and a domain having the function of the RING domain, which inhibits the activity of a caspase, wherein "the domain having the function of the BIR1 domain encoded by the nucleic acid has the amino acid sequence of residues 74 to 140 of SEQ ID NO:2, the domain having the function of the BIR2 domain encoded by the nucleic acid has the amino acid sequence of residues 182 to 249 of SEQ ID NO:2, and the domain having the function of the RING domain encoded by the nucleic acid has the amino acid sequence of residues 298 to 314 of SEQ ID NO:2". However, the specification, as originally filed, does not appear to provide written support for a genus of structurally variant nucleic acid molecules encoding variants of the polypeptide of SEQ ID NO: 2, which comprise these domains and inhibit the activity of any member of a genus of caspases.

Any, or all of these issue might be remedied if Applicant were to point to specific disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the present claims.

15. Claims 1-14, 19, 46, 70-83, and 90-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an *isolated*, recombinant nucleic acid comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1 and encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an *isolated* expression cassette molecule comprising the polynucleotide sequence of said isolated, recombinant nucleic acid, an *isolated* transformed cell comprising the polynucleotide sequence of said isolated, recombinant nucleic acid, and a method for making a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 by a process comprising culturing said isolated transformed cell, **does not reasonably provide enablement for making and using** a recombinant nucleic acid comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an expression cassette comprising a polynucleotide sequence that is at least

95% identical to SEQ ID NO: 1, or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, a transformed cell comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or a method for making a polypeptide comprising expressing a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

As explained in the above rejection of claims 1-14, 19, 46, 70-83, and 90-96 under 35 U.S.C. 101, the claims encompass, or are directed to the use of nucleic acid molecules, expression cassettes, and transformed cells, which have been introduced into cells comprised within an organism, including humans. Again, Support for this interpretation of the claims is found throughout the specification; see, e.g., paragraphs [0009]-[0011], [0055], [0063], and [0065]-[0074] of the published application.

However, as explained in section 10, beginning at page 18, paragraph 4, of the preceding Office action with regard to claims 13, 14, 17, and 19, the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to make and use the claimed invention without undue and/or unreasonable experimentation.

Notably it would be remedial to amend claims 1-14, 19, 46, 70-83, and 90-96, such that the claims are directed to "isolated" products, or to methods for making polypeptides, which, for example, comprise *culturing isolated* transformed cells.

Although the specification contemplates non-human transgenic animals, according to paragraph [0055] of the published application, for example, the transgenic animal is not necessarily a "non-human transgenic animal".

The specification does not provide a sufficient amount of guidance, direction, or exemplification to have enabled the skilled artisan, at the time the application was filed, to make or use transformed host cells containing the claimed nucleic acids or expression cassettes, which are comprised within a transgenic animals. As explained in

the preceding Office action, in the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predictable; nor is the transgenic embryo always viable. Houdebine (of record) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions; see entire document (e.g., paragraph bridging pages 272 and 273). Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable (page 27, column 1). Therefore, it is concluded that skilled artisan could not make and use the claimed invention, where the products are comprised within a transgenic animal, or wherein the process is performed in vivo within a transgenic animal, without undue experimentation and/or unreasonable experimentation.

Furthermore, as evidenced by Ayliffe et al. (of record), Day (of record), and Cellini et al. (of record) the preceding Office action similarly explained that the state of the art of producing transgenic animals, the level of skill in the art, and the unpredictability associated with the art is such that the amount of guidance, direction, or exemplification would not be sufficient to have enabled the skilled artisan, at the time the application was filed, to make or use transformed host cells containing the claimed nucleic acids or expression cassettes, which are comprised within a transgenic plant.

Turning now to new issues, because of the breath of claims, which are reasonably interpreted to encompass products that are comprised within a human, it is noted that the specification does not provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to produce the claimed host cells comprised of the claimed nucleic acids and expression cassettes within a living organism by gene transfer, or *gene therapy.* The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully

making and using the claimed invention without need of performing undue and/or unreasonable experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teaches that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional and an undue amount of experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable expectation of success without having the need to perform an undue amount of experimentation.

This issue can be remedied by amending claims 1-8 and 70-73 such that they are solely directed to "isolated", as opposed to "recombinant", nucleic acid molecules, "isolated" expression cassettes, "isolated" transformed cells, and methods for making recombinant polypeptides comprising *culturing isolated* cells comprising the nucleic acid molecules encoding the polypeptides.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application

filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 1-8, 44, 70-73, and 84-89 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication 2001/0053519 A1.

Claims 1-8 and 70-73 are drawn to an isolated or recombinant nucleic acid comprising at a polynucleotide sequence (i.e., at least 2 contiguous nucleotides) that is at least 95% identical to SEQ ID NO: 1, or encodes a polypeptide comprising a sequence (i.e., at least 2 contiguous amino acids) of SEQ ID NO: 2. Claims 44 and 84-89 are directed to an array comprising an isolated or recombinant nucleic acid comprising at a polynucleotide sequence (i.e., at least 2 contiguous nucleotides) that is at least 95% identical to SEQ ID NO: 1, or encodes a polypeptide comprising a sequence (i.e., at least 2 contiguous amino acids) of SEQ ID NO: 2.

U.S. Patent Application Publication 2001/0053519 A1 "n-mer arrays" comprising a solid support to which are attached all possible nucleic acid sequences of a given length, such as, and including a 10-mer array; see entire document (e.g., page 10, paragraph [0101]).

The n-mer arrays (e.g., the array of 10-mers), which are disclosed by U.S. Patent Application Publication 2001/0053519 A1, comprise isolated polynucleotides comprising any number of contiguous nucleotides of the polynucleotide sequence set forth as SEQ ID NO: 1, which encode any number of contiguous amino acids of the amino acid sequence of SEQ ID NO: 2.

18. Claims 1-10, 12-16, 19, 46, 70-83, and 90-95 are rejected under 35 U.S.C. 102(a) as being anticipated by Huang et al. (*Biochimica et Biophysica Acta.* 2001; **1499**: 191-198) (or record).

Huang et al. teaches an isolated nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; see entire document (e.g., the abstract; and page 194, column 1). Huang et al. teaches the messenger RNA (mRNA) from which the isolated complementary DNA (cDNA) molecule encoding the protein was isolated from BmN

cells (see, e.g., page 192, column 2). Huang et al. teaches the polypeptide encoded by the isolated nucleic acid molecule comprises a BIR1 domain that spans amino acids 74-140, a BIR2 domain that spans amino acids 182-249, and a RING domain that spans amino acids 298-314 of its amino acid sequence; see, e.g., page 193, Figure 1. Huang et al. teaches the polypeptide inhibits the activity of caspase-9; see, e.g., page 196, column 1. Huang et al. teaches the polypeptide inhibits apoptosis in insect cells, such as *Spodoptera frugipera* cells; see, e.g., page 194, columns 1 and 2. Huang et al. teaches the polypeptide inhibits apoptosis induced by Bax in mammalian cells; see, e.g., page 195, columns 1 and 2. In addition, Huang et al. teaches a transformed cell (i.e., a bacterial cell, a mammalian cell, or an insect cell, or more particularly a *Spodoptera frugipera* (Sf)-21 cell) comprising an expression cassette comprising the polynucleotide sequence of the isolated nucleic acid molecule, which encodes the polypeptide; see, e.g., page 192, column 2. Huang et al. teaches making the polypeptide by a culturing the transformed cell that expressed the polynucleotide sequence encoding the polypeptide; see, e.g., page 193, columns 1 and 2. Huang et al. teaches bacterial cells comprising an expression cassette comprising a polynucleotide sequence encoding the amino acid sequence of the polypeptide, wherein the expression of the polynucleotide sequence is regulated by an inducible promoter; see, e.g., page 192, column 2.

Although Huang et al. does not teach the polypeptide encoded by the isolated nucleic acid molecule is capable of inhibiting apoptosis in plant cells, because the polypeptide described by the prior art is "BmIAP", absent a showing of any difference, the polypeptide disclosed by the prior art and the polypeptide encoded by the claimed nucleic acid sequence are deemed the same. Accordingly, the nucleic acid disclosed by the prior art and the nucleic acid of claim 5 are deemed the same.

Conclusion

19. No claim is allowed.

20. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. U.S. Patent No. 6,570,069 teaches a nucleic acid comprising a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1, wherein said nucleic acid encodes a polypeptide that inhibits the activity of a caspase. WO 200159108 A2 teaches a nucleic acid comprising a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1, wherein said nucleic acid encodes a polypeptide that inhibits the activity of a caspase.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
January 23, 2006